

RESEARCH PAPERS**Preliminary Experience with Dexmedetomidine in Neonatal Anaesthesia**

ÖZCENGİZ Dilek, GÜNES Yasemin, ATCI Mustafa

ABSTRACT

Background: In paediatric patients dexmedetomidine has been reported to be effective in various clinical settings including provision of sedation during mechanical ventilation, prevention of emergence delirium after general anaesthesia, sedation during non invasive radiological procedures. However very few data of its use in newborn is available.

Patients & Methods: Sixteen new born patients of age 2-28 days were studied. Anaesthesia was induced with 1 mgkg⁻¹ ketamine intravenously. Dexmedetomidine 1 µgkg⁻¹ was infused within ten minutes. Maintenance infusion was started as 0.5-0.8 µg kg⁻¹h⁻¹ until the end of surgery or tracheal intubation was done all patients were mechanically ventilated with O₂+H₂O vapour 0.1-0.2%. Non invasive systolic & diastolic blood pressure, heart rate, SPO₂, DETCO₂, inspired & end tidal sevoflurane concentration and body temperature were monitored.

Results: No significant difference was observed in the measured values of haemodynamic parameter at different intervals and the base line values. No patient had hypotension bradycardia hypertension hypoxia or respiratory depression. Patients had mild hypothermia during post-operative period.

Conclusion: Dexmedetomidine 1 µgkg⁻¹ followed by maintenance dose of 0.5 µg kg⁻¹h⁻¹ as an adjunct to sevoflurane anaesthesia in new born undergoing laparotomy provides haemodynamic stability during heightened surgical stimulation.

KEYWORDS: Dexmedetomidine, Neonatal anaesthesia

Dexmedetomidine is a selective and potent α₂-adrenoceptor agonist, with hypnotic, analgesic and sympatholytic properties.¹ In surgical patients, it reduces the use of other anaesthetics, minimizes sympathetic response to nociceptive stimuli and improves intraoperative hemodynamic stability.¹

In contrast with many anaesthetic agents, dexmedetomidine preserves spontaneous ventilation. This property makes dexmedetomidine a useful adjuvant to general anaesthesia during procedures requiring spontaneous ventilation, such as upper airway surgery and manipulation.² One case report described administering dexmedetomidine as the only anaesthetic for three adults needing upper airway operations.³ Also Shukry et al⁴ reported that dexmedetomidine was useful anaesthetic agent in children's anaesthesia. In the paediatric population, dexmedetomidine has been reported effective in various clinical scenarios, including the provision of sedation during mechanical ventilation, prevention of emergence delirium after general anaesthesia, procedural sedation during noninvasive radiologic procedures, including magnetic resonance imaging, and in the control of withdrawal after the prolonged use of opioids and benzodiazepines.⁵⁻¹³

But, there are very few data related to dexmedetomidine

in newborn patients.

This study aimed to assess hemodynamic responses to nociceptive stimuli when dexmedetomidine is used as an adjuvant anaesthetic to sevoflurane in newborn patients submitted to surgery for laparotomy.

PATIENTS AND METHODS

We prospectively studied the charts of full term neonates (born at 37 weeks of gestation or more, and less than 29 days old), who underwent general anaesthesia, using dexmedetomidine and sevoflurane, for abdominal surgical procedures in the paediatric operating theatre of a University Hospital between October 2008 and March 2009.

The Ethics Committee of our institution approved the study and informed consent was obtained from the parents of all selected subjects. Exclusion criteria were the presence of major congenital malformations, birth weight <1000 g, previous or concurrent use of opioid for any reason (caesarean section with general anaesthesia), hemodynamic instability before the indication of tracheal intubation and refusal of the parents to enroll the neonate in the study.

Twenty newborns were studied, but four patients were excluded due to deep bradycardia. These patients were

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given atropin sulphate $40 \mu\text{g kg}^{-1}$. After this observation, we changed the study protocol and anesthesia was induced 1 mg kg^{-1} ketamine in all neonates. Dexmedetomidine ($1 \mu\text{g kg}^{-1}$) was infused during 10 minutes and maintenance infusion was obtained with dexmedetomidine ($0.5\text{--}0.8 \mu\text{g kg}^{-1} \text{h}^{-1}$) until the end of surgery. Cardiorespiratory monitoring included noninvasive blood pressure, [systolic arterial pressure (SAP), diastolic arterial pressure (DAP)], electrocardiogram and heart rate (HR), peripheral oxygen saturation (SpO_2), exhaled carbondioxide (PETCO_2), inhaled and end-tidal sevoflurane concentrations. Body temperature was monitored by an esophageal thermometer. Patients were intubated (oro-tracheal intubation) and mechanically ventilated with 65% N_2O in 35% O_2 during the anesthesia. Sevoflurane was administered 0.1 - 0.2 %. Mechanical ventilation was adapted to maintain an end-tidal CO_2 level of 33–36 mmHg and SpO_2 in the range of 95–100%. We recorded measurements of hemodynamic parameters during the anesthesia. These data were assessed before anesthesia induction and maintained every 5 min during the operation time.

Adjustments were predefined to prevent hypotension and low cardiac output, as well as to provide adequate analgesia.

- If systolic blood pressure decreased (equal to or greater than 20% of baseline levels) infusion solution was infused for 5 minutes and repeated up to three times, if hypotension persisted;
- If systolic blood pressure decreased (equal to or greater than 30% of baseline levels) dexmedetomidine infusion was reduced by 50%. If blood pressure levels did not reach at least 20% of baseline levels, intravenous administration of dexmedetomidine was discontinued.
- If the heart rate decreased more than 30% from baseline levels, a dose of $20 \mu\text{g kg}^{-1}$ intravenous atropine was administered.
- If systolic blood pressure and/or heart rate increased more than 20% from baseline levels, ketamine (1 mg kg^{-1}) was given at five-minute intervals. If systolic blood pressure and/or heart rate still increased more than 20% from baseline levels, anesthesia was maintained with sevoflurane 1-2 %. The endpoint was a maximal acceptable increment of 20% from baseline levels.

To evaluate the efficacy of the anesthesia regimen, the need for supplemental doses of ketamine or changes in the dexmedetomidine infusion rate were noted. Additional doses of ketamine (1 mg kg^{-1}) were administered only if the analgesia was inadequate and bradycardia present. Anesthesia was discontinued after finished operation. The trachea was extubated on resumption of spontaneous respiration and control of the airway. Time to extubation

was recorded in neonates. Extubation time is defined that skin suturation was finished to spontaneous respiration. All the newborns was heated externally using a blanket.

Statistical analysis was performed using SPSS version 11.0 software (SPSS Inc., Chicago, IL). DBP, SBP, HR and body temperature were compared using two-way repeated measures analysis of variance (ANOVA). All data were compared to baseline values. We accepted the baseline values as preoperative measurements. Unless otherwise specified, data are mean \pm SD, and p value <0.05 was defined as significance.

RESULTS

The cohort for the study included 16 newborn patients ranging in age from 2 to 28 days old (mean, 15.13 ± 14.93 days) and in weight from 1600 to 5300 g (3151.25 ± 954.93 g). Ten patients had intestinal atresia and six patients had intraabdominal tumors. The duration of operation was 2.3 ± 0.9 hours.

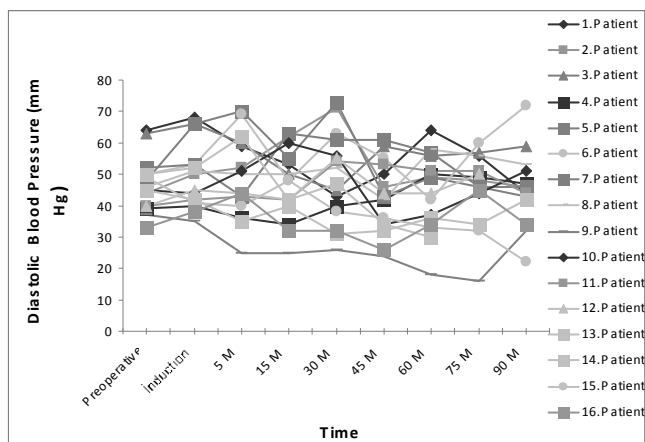
No significant differences were observed measurement intervals compared to the baseline levels in DBP, SBP and HR. Three patients needed supplemental ketamine doses only once. Sevoflurane concentration was 0.16 ± 0.05 %. No patient needed more than 0.2 % sevoflurane concentration. Comparing to the baseline values a remarkable decrease in temperature at all the observation times was not statistical significant. ($p > 0.05$). Mean effective dose was $0.5 \mu\text{g kg}^{-1} \text{h}^{-1}$. This dose obtained hemodynamic stability and effective anesthesia.

The duration of extubation was 16.1 ± 3.9 minutes (min=10, max=23 min). All the patients were extubated in the operation room and patients' breathing was satisfactory. After extubation the patients cried and opened the eyes.

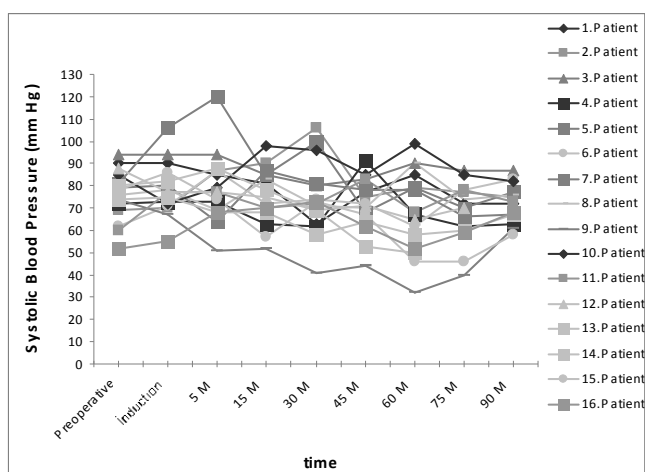
No patients had any hypotension, hypertension,

Table 1
HR, DBP, SBP and temperatures (Mean \pm Standard Deviation)

	HR	DBP	SBP	Temperature
Preoperative	136 \pm 18	50 \pm 8	76 \pm 11	36.0 \pm 0.7
Induction	143 \pm 17	50 \pm 10	78 \pm 12	36.0 \pm 0.6
5 min	150 \pm 16	50 \pm 13	76 \pm 16	35.9 \pm 0.6
10 min	148 \pm 19	50 \pm 10	79 \pm 15	35.9 \pm 0.7
15 min	148 \pm 17	47 \pm 11	75 \pm 8	35.7 \pm 0.9
20 min	149 \pm 19	44 \pm 14	76 \pm 12	35.7 \pm 0.7
25 min	149 \pm 19	47 \pm 12	76 \pm 14	35.6 \pm 1.0
30 min	147 \pm 17	49 \pm 14	73 \pm 15	35.7 \pm 0.9
35 min	145 \pm 19	49 \pm 12	74 \pm 16	35.6 \pm 1.0
40 min	143 \pm 18	46 \pm 11	73 \pm 17	35.5 \pm 0.9
45 min	142 \pm 20	43 \pm 11	74 \pm 14	35.4 \pm 0.9
50 min	145 \pm 18	43 \pm 16	71 \pm 12	35.4 \pm 1.0
55 min	144 \pm 18	45 \pm 13	66 \pm 11	35.3 \pm 1.1
60 min	143 \pm 18	44 \pm 12	70 \pm 14	35.3 \pm 1.0

**Figure 1**

Diastolic pressures of the patients during the operation (M:minutes)

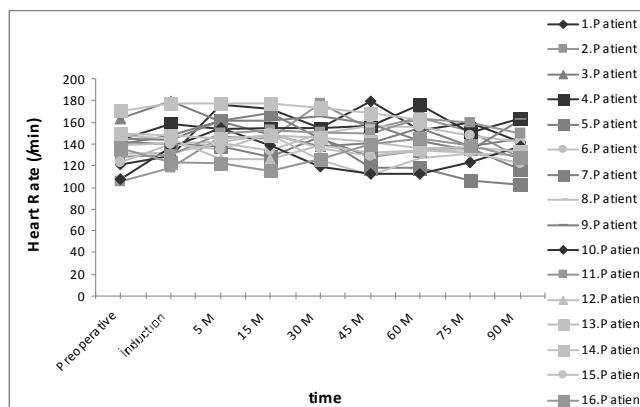
**Figure 2**

Systolic pressures of the patients during the operation (M:minutes)

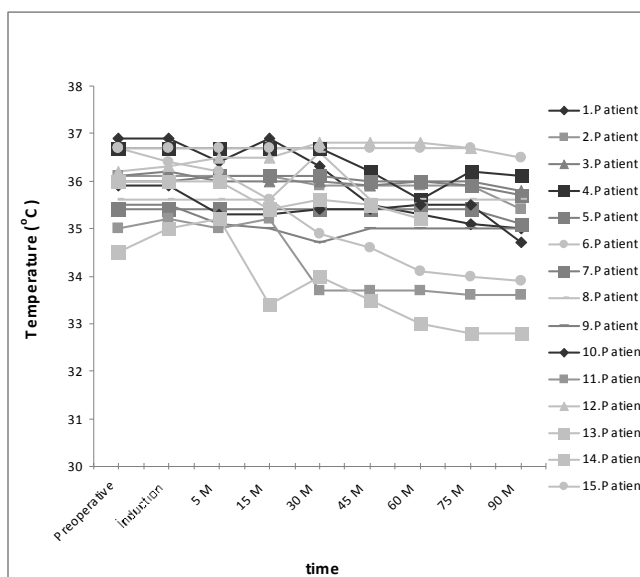
bradycardia, hypoxia and respiratory depression. The patients had mild hypothermia during the postoperative period. External heating was very difficult, however we did not observe any complication related to hypothermia.

DISCUSSION

In this study, dexmedetomidine with ketamine induction obtained very stable hemodynamic effect and very comfortable anesthesia in newborn anesthesia. Smania et al.⁵ reported that in their study, infusion of $0.5 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ of dexmedetomidine as isoflurane adjuvant at 1.2% allowed control of the hemodynamic response to stimuli with values equal to or less than those of the baselines, reflecting adequate control of the sympathetic stimulus in videolaparoscopic appendectomy. Some studies have described a remarkable decrease in the MAC of isoflurane, with lessening of consumption, when combined with the continuous infusion of dexmedetomidine, in plasma

**Figure 3**

Heart rates of the patients during the operation (M:minutes)

**Figure 4**

Temperature of the patients during the operation (M:minutes) rements were compared to the preoperative values

concentrations of 0.3 and 0.6 ng ml^{-1} .^{14,15} Munro et al.⁶ reported their experience with dexmedetomidine as the primary agent for sedation during cardiac catheterization in infants and children. The average maintenance infusion rate was $1.15 \pm 0.29 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ per hour (range, $0.6\text{--}2.0 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$). Tosun et al.⁷ compared dexmedetomidine and ketamine with propofol and ketamine in 44 children (age range, 4 months to 16 years) with acyanotic congenital heart disease undergoing cardiac catheterization. Ketamine ($1 \text{ mg}\cdot\text{kg}^{-1}$) and dexmedetomidine ($1 \mu\text{g}\cdot\text{kg}^{-1}$) were administered over 10 minutes followed by an infusion at $0.7 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ of dexmedetomidine and $1 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ of ketamine. Köroğlu et al.⁹ compared dexmedetomidine and propofol for sedation of children undergoing magnetic resonance imaging. The patients were taken to dexmedetomidine ($1 \mu\text{g}\cdot\text{kg}^{-1}$ followed by an infusion of $0.5 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$) and patients sedation was very effective.

In current study, we observed that dexmedetomidine with very low sevoflurane concentration obtained very smooth anesthesia with stable hemodynamic effect. Also anesthesia was enough to surgery, there were no response for surgical stimulation.

Mester et al.¹⁶ found that once the invasive/painful component of the procedure was completed, effective sedation could be provided by the dexmedetomidine infusion alone. In their study cohort, supplemental ketamine was required in only three patients (two patients when there was a need to change out the cannulae and in one other patient approximately 10 minutes after decreasing the dexmedetomidine infusion from 2 to 1 $\mu\text{g}\cdot\text{kg}^{-1}$ per hour). These results supported our findings, however our three patients needed supplementary ketamine dose only ones.

Suppression of hemodynamic response to nociceptive stimuli, with concomitant reduction of hormone release, is one of the major goals of an adequate "anesthetic state."¹⁷ Blood pressure and heart rate are the hemodynamic variables habitually used to assess the adequate block of the response to surgical stimulation.^{18,19} Similarly to what happens in adult patients, it was observed that during tracheal intubation dexmedetomidine induces lower increases of blood pressure levels and of the heart rate when compared to the placebo.^{15,20}

Vilo et al.²¹ reported that the pharmacokinetics of dexmedetomidine were clearly dependent on subject age in this study. Total plasma clearance was similar in younger and older children, but the volume of distribution (Vss) and consequently also the terminal elimination half-life ($t_{1/2,z}$) were greater in children younger than 2 yr of age compared with older children. There was, however, quite marked inter-individual variation in the pharmacokinetic parameters, especially in the younger age group. There is less experience reported for use of dexmedetomidine in infants, but in a recent larger study that included infants and neonates we found similar results with respect to respiratory depression.¹¹ Others have used dexmedetomidine for direct laryngoscopy and bronchoscopy in a small group of spontaneously breathing infants, as well as for cardiac catheterization in infants as young as 3 months of age.^{4,10} Ketamine was chosen as the agent for supplemental sedation. The reason for choosing ketamine was three-fold. First, ketamine has minimal negative effect on the systemic vascular resistance and has been shown to increase mean arterial pressure and heart rate.^{22,23} This theoretically could counteract the drop in mean arterial pressure and heart rate caused by dexmedetomidine.^{12,24} Second, ketamine has less negative effect on the respiratory drive when compared with opioids and benzodiazepines. Third, like with opioids and benzodiazepines dexmedetomidine has an additive

effect with ketamine.^{13,25} This allows for a much lower dose of ketamine needed for the same effect. A concern that many may have when using ketamine is its adverse effect of increased salivation. This is likely offset by dexmedetomidine's effect on the salivary glands causing xerostomia.²⁶ Given the relatively short duration of the procedures performed, dexmedetomidine was administered as a bolus at a rate of 0.2 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ without a maintenance infusion. Although some literature has shown that with acute intravenous administration, increases of approximately 20% in mean arterial blood pressure can occur, this was not observed in any of their patients.²⁷ Barton et al.⁸ reported that invasive procedures can be successfully performed in spontaneously breathing infants and toddlers with congenital heart disease using dexmedetomidine alone or in combination with low dose ketamine.

During the our study period, body temperature decreased compared to the baseline measurement. In our study, patients had no bradycardia. Probably, ketamine prevented this effect of dexmedetomidine. Finkel et al.²⁸ in a neonate, postulated that dexmedetomidine was the likely cause of hypothermia and subsequent bradycardia. Dexmedetomidine-induced bradycardia relates to its central sympatholytic action with unopposed vagal tone, reduction of noradrenaline release, or direct vagotonic effect and is usually reversed by anticholinergics.²⁹ In this patient, bradycardia was not reversed by atropine and was resolved only with correction of temperature in the continuing presence of dexmedetomidine. Dexmedetomidine affects thermogenesis by several mechanisms. In wild-type mice, dexmedetomidine causes profound hypothermia, an effect that is markedly attenuated in animals that are genetically deficient in $\alpha_2\text{-AR}$.³⁰ This hypothermic response is thought to result from the activation of $\alpha_2\text{-ARs}$ in the hypothalamus, reducing metabolic heat production.³¹ In infants, thermoregulation depends initially on vasoconstriction and increased metabolic heat production via nonshivering thermogenesis.^{32,33} Therefore, given the effects of dexmedetomidine on thermo regulation, it is not surprising that dexmedetomidine caused profound hypothermia in our patients. In a setting without active warming, dexmedetomidine can cause profound hypothermia in neonates. Careful attention to temperature control and the routine use of exogenous heat sources in infants receiving dexmedetomidine are imperative.

Many drugs in anesthesia conform to multiple compartment models and the time required for the plasma drug concentration to decline by 50% after terminating infusion (context-sensitive half-time) is markedly different from the elimination half-lives. Elimination half-life may be of limited value in characterizing disposition of intravenous

drugs during dosing periods relevant to anesthesia. Dexmedetomidine displays an increasing context-sensitive half-time with infusion duration because of return of drug to plasma from peripheral compartments after ceasing infusion. Potts et al.³⁴ demonstrated that there are age-related changes in the context-sensitive half-time with it taking 1.24 h for plasma dexmedetomidine concentration to decrease by half in neonates compared with 0.49 h in adults after an infusion of 1 h. These changes are attributable to clearance maturation. In our study, all the newborns can be extubated after surgery. This result has showed that dexmedetomidine obtained early recovery from anesthesia, but dexmedetomidine blood level couldn't measure in this study.

The current study, showed that an initial dose of dexmedetomidine ($1 \mu\text{g}\cdot\text{kg}^{-1}$) followed by a maintenance dose of $0.5 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$, as an adjuvant to sevoflurane anesthesia, in newborn submitted to laparotomy, kept the heart rate and blood pressure stable, also in periods of heightened surgical stimulation. Nonetheless, larger prospective studies are needed to further evaluate its efficacy and safety in this patient population.

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